University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Synthesis of a Diaryliodonium Salt and Its Use in the Direct Arylation of Indole: A Two-Step Experiment for the Organic Teaching Laboratory

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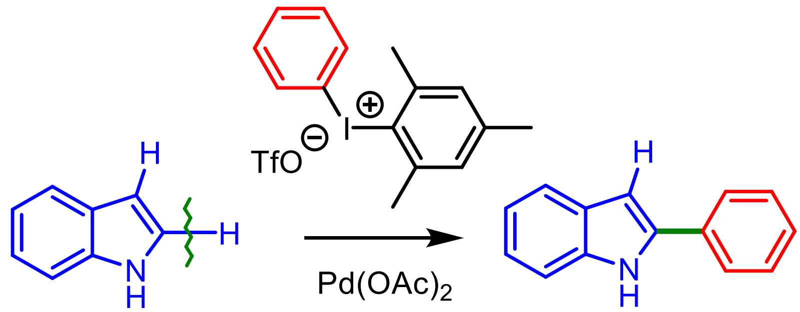
ABSTRACT

In the last decade, C—H functionalisation has been a very active topic of research in both academia and industry. When a H atom is replaced by an aryl (or heteroaryl) group, the transformation is termed 'Direct Arylation'. This approach to the formation of key (hetero)aryl-(hetero)aryl bonds is complementary to traditional methods such as the Suzuki-Miyaura and Stille reactions. Direct arylation/C—H functionalisation is not represented in the majority of undergraduate chemistry laboratory curricula. An experiment is described here in which students carry out a multi-step process, by synthesizing a diaryliodonium salt and using it in the direct arylation of indole. Important organic and organometallic chemistry concepts are covered, including catalysis, traditional cross-coupling, C—H functionalisation, multi-step reaction processes and regioselectivity. The experiment was successfully carried out by third- and fourth-year students in two universities, over a two-year period (4 times in total). Both high-yielding and low-yielding chemical steps were encountered, and a number of pedagogical approaches evolved.

GRAPHICAL ABSTRACT



KEYWORDS

Upper-Division Undergraduate, Organic Chemistry, Laboratory Instruction, Hands-On Learning/Manipulatives, Synthesis, Catalysis

INTRODUCTION

The formation of aryl-aryl and aryl-heteroaryl bonds are key transformations in organic chemistry.[1] The reaction can be carried out using well-known, named reactions such as the Suzuki-Miyaura,[2] Stille,[3] Negishi[4] and related processes. Indeed, Suzuki and Negishi shared the Nobel Prize in Chemistry in 2010 (along with Richard F. Heck) for their contribution to these types of reactions.[5] The aryl-heteroaryl products that arise from cross-coupling are very prominent throughout medicinal chemistry, and also in the agrichemical and energy sectors (Figure 1).

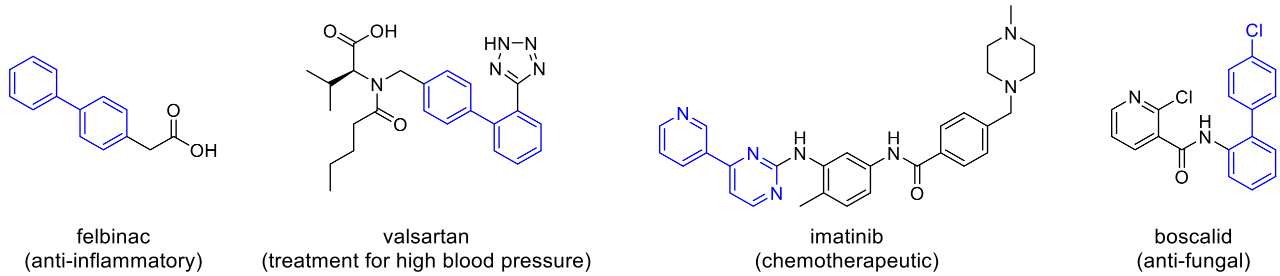


Figure 1. Important compounds containing key aryl-aryl bonds and their heterocyclic counterparts. (Het)aryl-(Het)aryl moieties in blue.

The Suzuki-Miyaura and related reactions can be executed under mild reaction conditions, in excellent selectivity and yields[6] and these transformations have been carried out at the undergraduate level, and very successfully.[7]

Despite the broad usefulness of traditional cross-coupling reactions, they require the installation of an activating group on each coupling partner (Figure 2 (i)). For example, Suzuki-Miyaura coupling usually involves a boronic acid and an aryl halide, and Stille coupling utilizes tin-based reagents and aryl halides. The installation of these activating groups has time and cost implications, especially on a large scale. There is also the associated waste, post-reaction. Tin-based residues, in particular, are usually toxic and their disposal has environmental issues.[8]

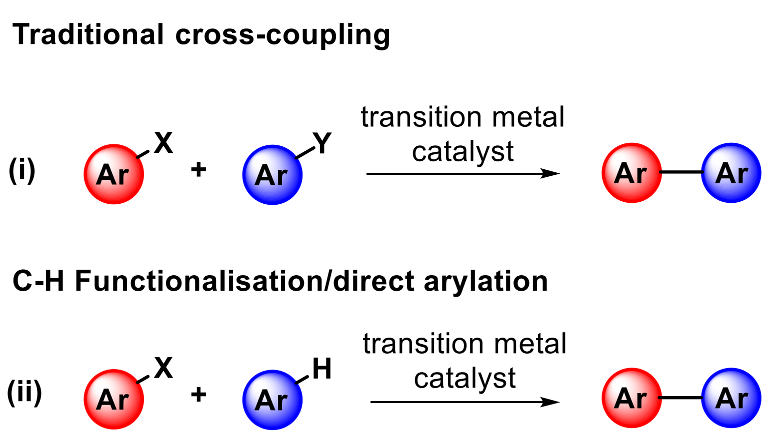


Figure 2. Traditional cross-coupling and C—H functionalisation (X=halide, Y=boronic acid, stannyl group etc)

In the last decade, organic chemists have begun to replace one (or sometimes both) reactants with 'unactivated' coupling partners (Figure 2 (ii)). The unactivated coupling partner contains a C—H group, and the H is substituted in the reaction process. The methodology is termed 'C—H activation or C—H functionalisation'.[9] The direct functionalisation of the C—H group in cross-coupling has a number of major advantages:

1) The substrate does not have to be pre-activated;

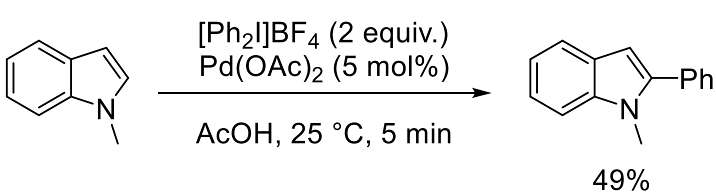
2) The waste is 'H' which can usually be picked up in its H^+ form using base, thus it can present fewer environmental concerns;

3) Direct C—H functionalisation can provide advantages in situations where halogenated, borylated or stannylated coupling partners are difficult to prepare;

4) Due to the number of C—H bonds present in many molecules of biological relevance, and because chemists are continuing to develop new C—H functionalisation chemistry, molecular entities which are difficult to prepare via traditional cross-coupling can become accessible.

However, there are many challenges in the field of C—H functionalisation. For example, in aryl (and often in heteroaryl) compounds, the C—H bond is quite strong and thus can be difficult to cleave.

Indoles comprise the structural core of many biologically active natural (e.g. serotonin, a neurotransmitter) and unnatural (e.g. sertindole, an anti-psychotic drug) compounds.[10] Aryl indoles, in particular, are prevalent in a range of therapeutics.[11] Initial work by Sanford (Scheme 1),[12] Gaunt[13] and others demonstrated that certain C—H bonds in indole could be broken using transition metal catalysts, and coupled with aryl iodonium salts to form new C—C bonds. Aryl iodonium salts[14] involve iodine in a +III oxidation state, which has the consequence of making the attached aryl group quite reactive.



Scheme 1. Sanford and co-workers showed that indoles could be arylated under mild conditions.[12]

Since the seminal publications, a number of groups have reported alternative reaction conditions. For example Malmgren *et al.*[15] published the arylation of indoles at the 2-position, in water. Fairlamb and co-workers carried out C—H functionalisation reactions on tryptophan-derivatives without the need for acidic solvents, base or additional oxidants.[16]

Herein, a laboratory experiment involving the synthesis of a diaryliodonium salt and its application in the direct arylation of indole, is described. This experiment is aimed at students at an upper undergraduate or Masters of Science level. It was undertaken by four sets of undergraduate chemistry students at University College Cork (UCC), Ireland and at Technische Universität Wien (TU Wien), Austria over two academic years.

During the experiment, the students synthesized the diaryliodonium salt and employed the salt in the Pd-catalyzed arylation of indole. The pedagogical goals that we aimed to achieve, and the learning outcomes that we envisaged for the participating students through conducting this experiment, are listed and described in detail in the SI.

HAZARDS

Students must wear safety glasses, lab coats, and gloves. These reactions should be performed in a fume hood or similarly well-ventilated workspace. The experiment must be fully risk-assessed by all participants. This was performed as part of a pre-laboratory assessment to ensure compliance. PIDA and sodium bicarbonate are not classified as hazardous substances or mixtures, although caution should always be taken. Mesitylene, diethyl ether and ethyl acetate are flammable and can cause skin and respiratory irritation, as well as dizziness on inhalation. Trifluoromethanesulfonic acid is corrosive. Dichloromethane causes skin and serious eye irritation and may cause respiratory irritation and damage to organs. The diaryliodonium salt synthesized causes skin and serious eye irritation, and may cause respiratory irritation. Indole is toxic in contact with skin, causes skin and serious eye irritation and may cause respiratory irritation. Palladium(II) acetate causes serious eye damage. Chloroform-D3 is a potential carcinogen, harmful if swallowed, causes skin and serious eye irritation, is toxic if inhaled and causes damage to organs.

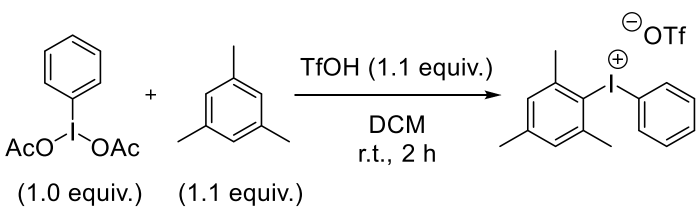
EXPERIMENTAL OVERVIEW

In summary, the diaryliodonium salt synthesis and subsequent direct arylation reaction were carried out without the need for specialized glassware or prior purification of reagents/solvents. The diaryliodonium salt prepared in step 1 did not require purification prior to use, and the direct arylation product was purified using flash column chromatography in step 2.

Course instructors can tailor the experiment to suit their needs, allowing them to highlight themes from the experiment that are relevant to their pedagogical goals and course content.

The two parts of the laboratory experiment were completed across 3 x 3-hour laboratory sessions. This, along with the scientific content, makes it an ideal exercise for third- and fourth-year undergraduates as part of a Bachelor of Science Degree, or for Masters of Science, or Master of Chemistry programme. Detailed experimental procedures can be found in the Supporting Information.

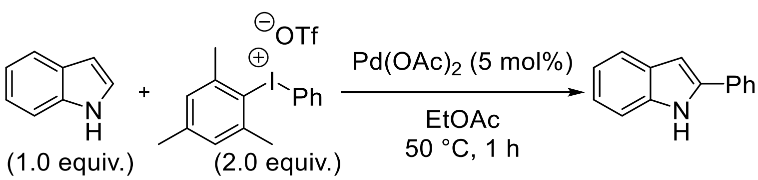
Diaryliodonium Salt Synthesis



Scheme 2. Synthesis of diaryliodonium salt.

The diaryliodonium salt was synthesized from commercially available phenyliodo(III)diacetate (PIDA), (Scheme 2).[15] PIDA and mesitylene were suspended in dichloromethane (DCM) and the suspension was cooled to 0 °C using an ice bath. Trifluoromethanesulfonic acid (TfOH) was added dropwise to the stirring mixture. Once addition was complete, the mixture was stirred for 2 h, then concentrated under reduced pressure. Diethyl ether (Et_2O) was added to the residue and a solid precipitated. The solid was isolated using a Büchner funnel and washed further with Et_2O until the filtrate ran clear of coloured components. The solid was left to dry in air in an oven at 65 °C for 1 h prior to use. Students were expected to obtain a yield of >90% from a well-executed experiment. Purity was checked by melting point and ^1H NMR spectroscopy. If desired, this step of the procedure could be performed in pairs, as an excess of diaryliodonium salt was usually obtained, relative to the amount required for the subsequent direct arylation step. The compound is a stable solid and can be stored at ambient temperature for extended periods of time. Additional tests showed the solid is stable at 65 °C for several days. This gives flexibility with regard to the scheduling of laboratory classes: Both reactions (Sessions 1 and 2) may be performed in one day, or scheduled over a couple of weeks.

Direct Arylation Reaction



Scheme 3. Direct arylation reaction.

The direct arylation reaction was performed using commercially available $Pd(OAc)_2$ and indole (Scheme 3). The conditions are based on reported conditions for the arylation of tryptophan derivatives.[16] None of the reagents or solvents were purified prior to use. The catalyst was employed at 5 mol% loading and ethyl acetate (EtOAc) was used as the solvent. The mixture was stirred at 50 °C for 1 h. Once consumption of starting material was confirmed by TLC, the reaction was cooled to ambient temperature. The organic layer was washed with a saturated solution of sodium bicarbonate and brine, dried over $MgSO_4$, filtered and concentrated onto celite under reduced pressure. The crude residue on celite was loaded onto a column of silica gel and the product was eluted with a mixture of EtOAc and cyclohexane in moderate yields (typical student yield was ca. 30%).

It should be emphasized to students that care must be taken to ensure complete removal of residual solvent. Some yields reported by students were inflated due to residual solvent and poor drying. Again this was recognised by students in their reports.

Following their experimental work, participating students completed written reports, which were structured to include a title, date, introduction, results, discussion, experimental section, and conclusion. Details of the NMR spectra used to establish product purity were included, as were details of the yields of the iodonium salt and 2-arylindole products.

Experimental Sessions at University College Cork (UCC), Ireland

At UCC, third-year undergraduate chemistry students undertook the experiment in 3 x 3-h sessions over 2 days. In the first year (2018) in which this experiment was run, nine students participated and worked individually. In the second year (2019), seventeen students participated and worked mainly in pairs. Very little difference was noticed between both cohorts and thus the results will be taken together. Laboratory demonstrators were on hand throughout, to assist the students if necessary. On the first day, students synthesized the diaryliodonium salt (Session 1, average yield 91%).

Results and Discussion

Two students obtained material which would correspond to yields >100% due to insufficient drying of the salt. This was recognized by both students in their reports. The melting point of the diaryliodonium salt was obtained by each student to confirm that the salt had been successfully synthesized. The ^{1}H NMR spectrum of the newly formed salt was also obtained by each student or student pair. A representative example of a ^{1}H spectrum obtained by a student is shown in Figure S1 in the SI.

Next (session 2), the students used the iodonium salt in the direct arylation reaction as described in detail in the SI, followed by an aqueous workup, and concentration of the organic layers onto celite for loading on to flash chromatography columns. On the second day (session 3), the students purified their products using flash chromatography. The ^{1}H NMR spectrum of each student's product was recorded. Of the nine students (Year 1), six successfully isolated the 2-phenylindole product from the crude reaction mixture. The yields ranged from 13 to 55%. A sample spectrum from one student is shown in Figure S3 in the SI. The success of the reaction was determined by ^{1}H NMR spectroscopy through comparison of the starting materials and the product spectra. In particular, students were able to recognise the shift in the C3 proton resonance, as well as the absence of the C2 proton resonance of the indole starting material compared to the arylated product. The increased complexity of the aromatic region was also noted by students. Finally, it was relayed to students that the purity of the final product would, in some cases, not be sufficient for publication in scientific research journals. For the students that did not isolate pure 2-phenylindole, the ^{1}H NMR spectra showed, in some cases, that the product was contaminated with either 2-mesitylindole (side-product), mesityl iodide (by-product), or a combination of both. Additionally, the NMR spectra of some students revealed residual solvent as a result of incomplete drying of the product, prior to measuring the yield and preparing the NMR sample. As such, some yields reported by students were inflated.

Experimental Sessions at Technische Universität Wien (TUW), Austria

At TU Wien, the two-step sequence was imbedded in the "Advanced Synthetic Chemistry" laboratory course, which is a mandatory course for fourth-year students pursuing a Master Degree in synthetic chemistry. Therefore, the students at TU Wien are effectively one year more advanced than the students at UCC. Eight students participated in each of the 2 years (16 in total) in which the experiment was run. In the aforementioned laboratory course, students prepare two polymer chemistry experiments, four organometallic experiments, and four mainstream organic experiments. Students are free to execute the 10 experiments in any order within a given time period, and so the experiments were not carried out on the same day by all students. The experimental procedure was identical to that used at UCC.

On average, the synthesis of the diaryliodonium salt gave 95% yield (88-99%). The purity of the compound was determined by ^{1}H NMR spectroscopy and results were similar to that reported at UCC.

The subsequent arylation of indole was carried out as per the procedure described and the results of this step were also comparable. As at UCC, the purification of the 2-phenylindole via column chromatography was challenging for students at TU Wien. The yields ranged from 10 to 39%. Two students obtained an unexpected high yield of >80%. However, it was quickly identified that this was due to the presence of some impurities, mainly resulting from incomplete drying of the product after column chromatography. In cases of sufficient drying, the spectra were similar to those obtained at UCC.

APPRAISAL OF ACHIEVEMENT OF PEDAGOGICAL GOALS AND LEARNING OUTCOMES

In order to enable evaluation of the extent to which the learning outcomes were achieved by students, we conducted pre- and post-experiment assessments of the 17 students in the UCC 2019 cohort in which they were asked to answer a series of questions (included on p. S17 – S20 of the SI) focused on the topics covered in our intended learning outcomes.[17] Comparison of students' answers to questions in the pre-experiment assessment (administered prior to the pre-experiment introductory lecture) with their post-experiment assessment answers enabled us to establish whether their understanding of several key concepts of relevance to intended learning outcomes 1 – 9 had been improved, specifically through their engagement in this experiment. In Figure 3 is shown a graphical summary of our conclusions on the achievement of intended learning outcomes 1 – 6 by this group of students. In Figure 4 is shown a similar graphical summary relating to pre- and post-experiment assessment questions of relevance to learning outcomes 7 – 9. Note that we did not attempt to assess students' prior knowledge of material relevant to learning outcomes 4 and 8, as we felt that it would be unreasonable to expect students of the target level to have experience of these relatively high level outcomes (analysis of reactions and NMR spectra of cross coupling or direct arylation products).

In general, we observed that students' prior knowledge of the material relevant to intended learning outcomes 1 – 3, 5 – 7 and 9 was very limited. Only a small percentage of the students were able to give satisfactory answers to pre-experiment assessment questions on any of the various topics covered (see Figure 3 and 4).

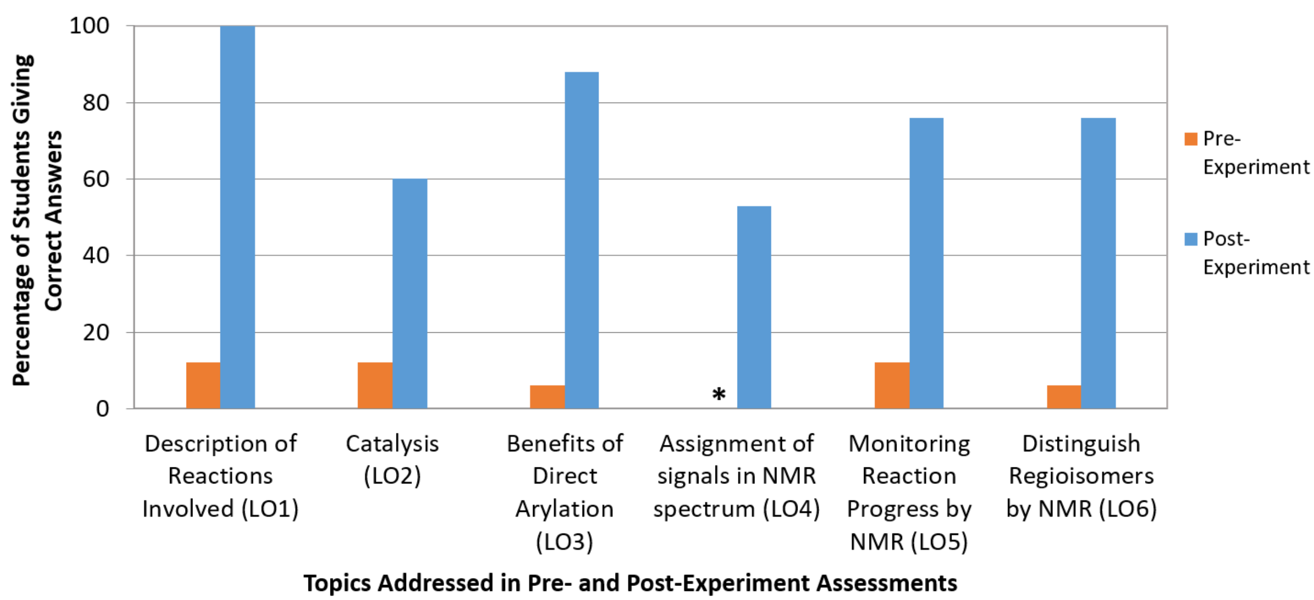


Figure 3. Bar chart showing student performance in pre- and post-experiment assessments questions relating to fulfilment of learning outcomes (LOs 1 – 6) for students from the UCC 2019 cohort. ***** We did not attempt to assess students' prior knowledge of interpretation and assignment of signals the ^{1}H NMR spectrum of the product. See main text for details.

The results displayed in Figure 3 show that learning outcomes 1, 3, 5 and 6 were achieved by at least 76% of the participating students (based on their answers to post-experiment assessment questions – see p. S17 – S20 in SI). Learning outcomes 2 and 4 were achieved by 60% and 53%, respectively, of the students involved. It can be seen from Figure 3 that significant improvements in students' understanding of the topics of learning outcomes 1 – 3 and 5 – 6 came about as a direct result of their engagement with the experiment and associated material.

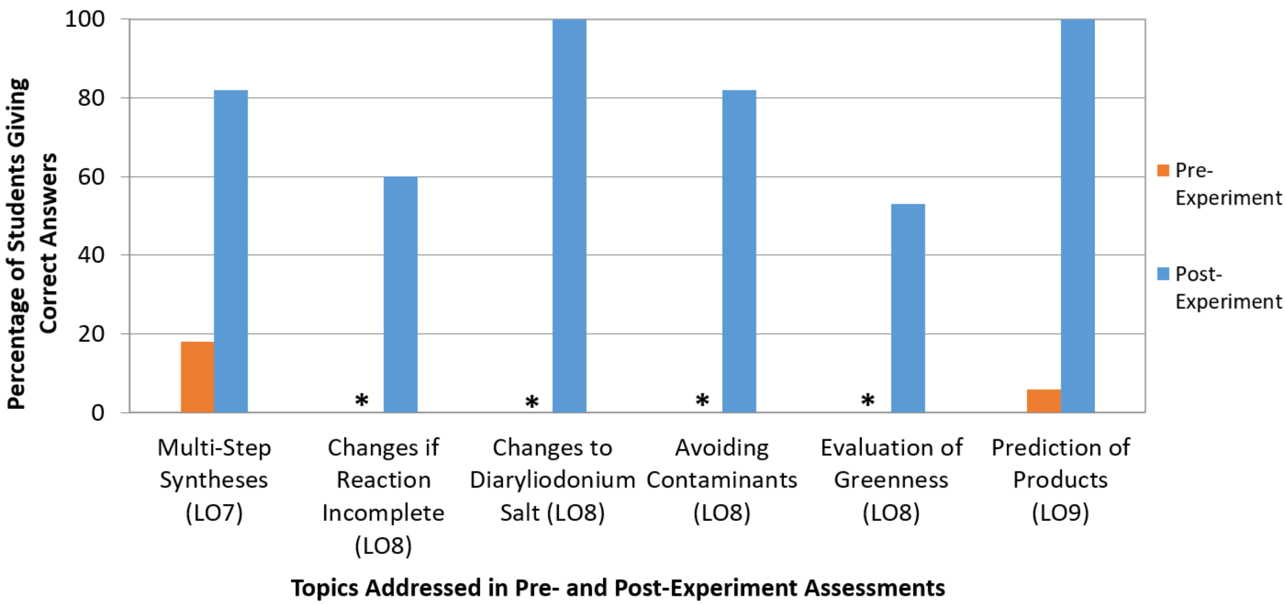


Figure 4. Bar chart showing student performance in pre- and post-experiment assessment questions relating to fulfilment of learning outcomes (LOs 7 - 9) for students from the UCC 2019 cohort. * We did not attempt to assess students' prior knowledge of these topics. See main text for details.

As shown in Figure 4, learning outcomes 7 and 9 were well achieved by this group of students (82% and 100%, respectively) based on their answers to questions 3 and 6 of the post-experiment assessment. Four questions relevant to learning outcome 8 were included in this assessment. These were intended to assess students' abilities to analyse the reactions they had carried out, in order to improve them – i.e. to discern what changes could be made to improve the yield, prevent side-reactions, avoid the presence of contaminants in the products, and evaluate the "greenness" of the process. All students identified suitable modifications to the structure of the diaryliodonium salt to minimize side-product formation, and over 80% were able to recognize potential contaminants that could be formed and suggest means of avoiding them. Only 60% put forward adequate suggestions for how to modify reaction conditions to improve the yield of the reaction. Although most students were capable of enunciating the benefits of the direct arylation process in the context of Green Chemistry, only 53% successfully identified drawbacks that compromise the "greenness" of this process, e.g. the use of diaryliodonium salt as a coupling partner, resulting in the formation of a stoichiometric amount of an aryl iodide by-product. Based on this, we conclude that learning outcome 8 was well achieved by 53% of the participating students, and partially achieved by most students (at least 82%).

Learning outcomes 7 – 9 were more challenging for students than learning outcomes 1 – 6. By demonstrating their abilities to evaluate the factors that dictate success in multi-step syntheses, analyse the reactions they had carried out, appraise potential improvements, and predict products of unfamiliar reactions (thereby fulfilling learning outcomes 7 – 9), the students demonstrated evidence of higher order thinking in the context of Bloom's taxonomy of educational objectives.[18]

Based on our analysis of these data, and the extent to which learning outcomes 1 – 9 were achieved by the 17 students involved in UCC in 2019, we conclude that pedagogical goals 1 – 3, 5 – 7, and 9 have been well achieved, while pedagogical goals 4 and 8 were partly achieved.

CONCLUSIONS

This laboratory experiment allowed students to work on a multi-step reaction, by synthesizing a diaryliodonium salt and using it in a subsequent direct arylation reaction. Important organic and organometallic chemistry concepts are covered, including catalysis, traditional cross-coupling, direct arylation/C—H functionalisation, multi-step reactions and regioselectivity. Techniques on which to focus on include NMR spectroscopy and TLC. The emphasis placed on each concept and on the analytical techniques can be at the instructor's discretion. This allows flexibility with respect to the availability of equipment, etc. The experiment can also be tailored to the needs of the student group.

The first part of the experiment demonstrated the synthesis of a diaryliodonium salt. Sufficient quantities were produced to allow this part of the experiment to be conducted in pairs if needed.

The second part of the experiment allowed the students to use the previously synthesised diaryliodonium salt in a direct arylation reaction. This aided the students' understanding of the importance of taking care with each synthetic step, as it can impact upon subsequent steps. A reaction carried out by a Demonstrator in the absence of palladium catalyst, showed that only the diaryliodonium salt and the indole starting material were present, as observed by TLC and ^{1}H NMR. This facilitated the students in understanding the role of a catalyst in an organic chemistry reaction. The direct arylation reaction can generate a mixture of arylated indoles, which were not always separated by the students after purification by flash chromatography. An example of a student's ^1H NMR spectrum after purification is shown in the SI. Students were able to assign key product ^1H NMR signals.

To conclude, this laboratory experiment was undertaken by undergraduate chemistry students at University College Cork, Ireland and at Technische Universität Wien, Austria over 2 years (4 times in total). The experiments can be used to demonstrate a number of important topics and analytical techniques in organic chemistry. As discussed, key topics include catalysis, traditional cross-coupling and C—H functionalisation, as well as NMR spectroscopy and TLC. Links can also be made to the movement towards more environmentally responsible organic synthesis, for example, the use of EtOAc as solvent, no added ligand, low reaction temperature and of course C—H functionalisation inherently avoids one activation partner. However, the C—H functionalisation step does utilise iodonium salts which is atom uneconomic, and thus there is scope for some in-class debate. As such, a variety of students should find the experiment engaging. The practical experience will help students in their understanding of what can be challenging techniques to adequately portray in lectures. For example, students performed work-ups and column chromatography. The latter in particular proved an excellent training output. Given the yields were moderate, separation of the pure arylated indole was challenging, yet importantly mimics many of the necessary purifications encountered on a daily basis in research laboratories. The range of concepts and techniques employed gives the instructor a lot of flexibility to tailor the laboratory experience to best suit their course content.

ASSOCIATED CONTENT

Supporting Information

Instructions for students, safety information, sample preparation (^1H and ^{13}C NMR spectroscopy) and notes for instructors (PDF).

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17. Two different approaches to these assessments were employed. Details on the first approach are included in the Instructors' Notes section of the Supporting Information for readers interested in the development of our assessment plan. The second of these approaches, described in the main text, was informed by our observations obtained from the results of the first approach.

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